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| (54) Title: PHARMACEUTICAL COMPOSITION CONTAINING DERIVATIVES OF SEX HORMONES (57) Abstract A pharmaceutical composition having a form suitable for transmucosal administration containing 17 β -estradiol and a compound selected from the progestins as active ingredients. | | |

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PHARMACEUTICAL COMPOSITION CONTAINING DERIVATIVES OF SEX HORMONES

5

Background of the invention

The present invention relates to a pharmaceutical composition having a form suitable for transmucosal administration and containing a combination of two lipophilic drugs which are one sex hormone and one derivative of a sex hormone. The present invention also relates to the use of this pharmaceutical composition in the treatment of postmenopausal disorders and osteoporosis.

15 Background art

Administration of estrogens is a common medical treatment for postmenopausal disorders and osteoporosis. Unopposed estrogen therapy, however, is known to increase the risk of endometrial carcinoma and hyperplasia and to increase the incidence of irregular bleedings as negative side-effects. Therefore, in addition to estradiol and its derivatives, progestin has been strongly recommended in therapy to protect against an estrogen-mediated increased risk of such negative side-effects. The dose of progestin should result in a sufficient plasma level to provoke the changes of the endometrium.

25

Postmenopausal disorders and osteoporosis require long-term medical treatment and it is, therefore, desirable to keep administered doses as low as possible and to include as few components as possible into pharmaceutical compositions in order to avoid undesired side-effects.

Sex hormones and derivatives of sex hormones are substances which are very potent with respect to their biological activity. One major problem in the use of such substances as drugs is to administer very small amounts of the drug to the patient at metered doses. This problem is particularly pronounced in cases where
5 the first pass mechanism via the intestinal mucosa must be circumvented.

Due to degradation during first pass metabolism in the liver, natural sex hormones have a poor bioavailability. The problem of low bioavailability can be overcome by alternative ways of administration circumventing the first pass
10 metabolism in the liver. Pharmaceutical compositions for nasal or buccal administration of the natural form of single sex hormones have been disclosed in EP 349091, US 4,383,993 and US 4,596,795 (see below).

Compositions for oral administration of estradiolvalerate and medroxyprogesterone acetate have been disclosed in EP 461290. The doses of sex hormone and
15 sex hormone derivatives in this composition are very high and the first pass mechanism of the estradiol valerate is not circumvented.

Parenteral administration circumvents the undesired first pass effect. There are,
20 however, obvious inconveniences associated with parenteral, for example intravenous or intramuscular drug administration such as the need for sterile delivery devices, pain and irritation caused by reiterated injections and the potential risk for infections. Another disadvantage is that the patient normally needs medical assistance in administering.

25

Transdermal drug delivery as another parenteral route implicates the risk of skin irritations. It also leaves very limited possibilities to adjust the dose and frequency of application to all therapeutic goals and individual needs.

Another alternative is drug administration via the transmucosal route. However, just as in the case with other methods for non-invasive medication the bioavailability of a drug after transmucosal administration is largely unpredictable, depending inter alia on the chemical nature of the drug and the drug delivery system.

Attempts have been made to design transmucosal, preferably nasal drug delivery systems of natural sex hormones, for example:

- 10 In J.Clin. Endocrinol. Metab. 45, 1977, pp. 1261-1264, Rigg et al. it has been demonstrated that intranasal administration of estradiol in a physiological saline solution is unsuitable.

15 In U.S. Patent No. 4,383,993, Hussain et al. suggested an aqueous solution of the sex hormones in isotonic saline containing a surfactant such as Tween 80 as a solubilizer. Because of its apolar character this adjuvant must be conceived as accomplishing the dissolution of the active substance in a monodispersed hydrophilic system. Systems containing such solubilizers often do not fulfill the required therapeutical needs. The reason for this is that, due to the limited
20 solubilization capacity, the required solubilizer concentration causes irritation of the mucosa or, as in the case of nasal administration, the volume to be applied is too high.

In EP 349091 it is stated that the use of dimethyl-b-cyclodextrin as an absorption
25 enhancer together with estradiol or progesterone in a solution, ointment or gel ensures a suitable drug delivery system for nasal administration of natural sex hormones. This system is known to have major disadvantages connected with dimethyl-b-cyclodextrin because of its nephrotoxicity and haemolytic activity. It can also be expected that the extremely high complex binding constant of the
30 cyclodextrin-sex hormone complex may adversely influence the drug uptake. This has, indeed, been proven to be the case in animal tests. For sublingual and buccal

administration, however, the use of dimethyl- β -cyclodextrin in sex hormone compositions has virtually no effect on the absorption according to U.S. Patent No. 4,596,795 (Pitha). This, according to the same inventor, is in contrast to the uptake from aqueous poly- β -cyclodextrin and hydroxypropyl- β -cyclodextrin. This
5 inventor stresses that a dissolved form of the natural sex hormones does not per se guarantee effective uptake through mucous membranes.

The use of an emulsion for nasal application is known from EP 272097. This patent refers to nasal administration of pharmacologically active polypeptides together
10 with a phospholipid such as a phosphatidylcholine, which is a lecithin, preferably admixed with a vegetable oil. The resulting system is characterized in that the water soluble active drug is located in the coherent, hydrophilic outer phase of a two phase system consisting of oil in water. A lecithin which is described in detail in this patent is used as an adjuvant which is effective in promoting the
15 polypeptide uptake. The addition of a vegetable oil is useful for stabilizing the emulsion.

The above mentioned negative side-effects of the use of sex hormones necessitate special attention with respect to the dose of the drug to be used. The dose should
20 be kept as low as possible, while assuring at the same time an effective level.

Synthetic derivatives of sex hormones orally administered can be utilized as a way of obtaining a higher bioavailability than by oral administration of the natural sex hormones. For example many synthetic derivatives of progesterone,
25 which are less susceptible to hepatic metabolism, show better efficacy upon oral administration than does the natural hormone itself. However, as it has been noted in the aforementioned EP 349091, US 4,383,993 and US 4,596,795, negative side-effects have been observed upon administration of synthetic derivatives of sex hormones. Such side-effects depend both on the dose and the structure of the
30 molecule of the sex hormone derivative.

Progestins have very different specific individual activities even if administered in the same way. This is illustrated in Table 1 where the therapeutic oral doses for some progesterone derivatives in combination treatment with estrogens are presented. These figures are doses generally recommended for therapeutic purposes.

Table 1

| <u>Progestins</u> | <u>Therapeutic dose (mg)</u> |
|----------------------------------|------------------------------|
| Progesterone | 200 - 300 |
| Dydrogesterone | 10 - 22 |
| Medroxyprogesterone acetate | 2.5 - 10 |
| Medrogestone | 5 |
| Chlormadinone acetate | 2 |
| Norethindrone acetate | 0.35 - 1.25 |
| Levonorgestrel (D(-)-Norgestrel) | 0.075 - 0.15 |
| Desogestrel | 0.075 - 0.15 |
| 3-Keto-Desogestrel | 0.010 - 0.15 |
| Gestodene | 0.010 - 0.15 |

The progestins are classified as follows:

- Derivatives of progesterone and 17 α -hydroxyprogesterone and (9 β ,10 α)-6,7-didehydroprogesterone. Representatives of this group are medroxyprogesterone acetate, dydrogesterone, medrogestone, chlormadinone acetate and megestrol acetate.

- Derivatives of 19-nortestosterone. Representatives of this group are norethindrone, norgestrel, levonorgestrel, desogestrel, 3-keto-desogestrel, gestodene.

- 5 The derivatives of 19-nortestosterone exert higher specific activities than the derivatives of progesterone and 17 α -hydroxyprogesterone.

In combination drugs one major problem resides in the different chemical character of the drugs to be administered. Different solubility properties
10 contribute to making the preparation of the combined drug difficult and to limiting the number of combinations of drugs and solvents. Yet another difficulty in combination drugs is the respective specific activity of the different drugs sometimes making it necessary to distribute very different amounts of two or more drugs.

- 15 Two-phase liquid systems suitable to solve this problem often require additives such as emulsifiers and/or preservatives in order to retain their physical and microbial stability. Such emulsifiers are often not well tolerated by mucosa and their use can result in damages of the mucosal membranes. The amount of such
20 additives therefore, needs to be kept low.

DE 4019670 discloses a drug which is a mixture of estrogen with chlormadinone acetate for the treatment of the postmenopause of woman ("Behandlung der Wechseljahre der Frau"). There is, however, in DE 4019670 neither any indication
25 as to how to solve the problem of administering the combination of drugs nor as to how to prepare such a pharmaceutical preparation nor how such a preparation is constructed.

WO 93/21924 claims a pharmaceutical composition containing at least one
30 precursor of testosterone which is applied nasally as a dosing spray. There is,

however, no indication as to how such a pharmaceutical composition is constructed nor manufactured.

5 WO 93/24107 discloses the use of a metered dose spray for nasal application of sex hormones and their derivatives according to this publication. The aim of the metered spray of WO 93/24107 is to keep the dose of active substance low and to facilitate the penetration of the hormone through the blood-brain barrier in order to treat central nervous system diseases. There is, however, no indication as to the composition of the formulation or as to how to prepare the formulation.

10

Medical emulsions as drug carriers are known from several patents. In EP 391369 emulsion systems are used as vehicles of delivery of lipophilic drugs. Only by combining three different groups of surfactants comprising phospholipids, a non-ionic surfactant and a cholic acid derivative a very small particle size and an
15 outstanding long term stability was obtained. The emulsions are for topical, parenteral and oral administration. However, surfactants, especially ionic surfactants are irritant to mucosa and are, therefore, less suitable for transmucosal administration of drugs and there is nowhere any indication as to how these emulsions can be administered transmucosally.

20

In EP 215313 an emulsion system for a certain hydrophobic drug comprising a combination of a surfactant, a co-surfactant and benzyl alcohol as a co-solvent is disclosed. There is, however, no indication of the use of this emulsion for transmucosal or nasal application of the drug. Also, the emulsion system of EP
25 215 313 requires both a co-surfactant and, as a co-solvent, benzyl alcohol.

Detailed description of the invention

The present invention provides a pharmaceutical composition for transmucosal administration characterized in comprising a pharmaceutical composition for
5 transmucosal administration, which composition is an oil-in-water emulsion containing, dissolved in the dispersed oil phase, the natural sex hormone 17β -estradiol together with a progestin which is selected from the group consisting of progesterone derivatives, 17α -hydroxyprogesterone and its derivatives, $(9\beta, 10\alpha)$ -6,7-didehydroprogesterone and its derivatives, and 19-nortestosterone and its
10 derivatives.

In another aspect the present invention provides a dosage form which is flexible with respect to the need of different concentration levels of the two active ingredients of the pharmaceutical composition.

15

In another aspect the present invention provides a pharmaceutical composition for the effective treatment of postmenopausal problems and osteoporosis while minimizing negative side-effects otherwise provoked by too high doses of the progesterone derivative part of said composition.

20

In another aspect administration of compositions of the present invention avoids irritation of the mucosa otherwise provoked by solubilizers and/or preservatives thereby minimizing damage to mucosal membranes caused by long-term use of said compositions.

25

In another aspect administration of compositions of the present invention avoids degradation of the hormone and the hormone derivative component of the pharmaceutical composition by first pass metabolism in the liver as far as this is considered relevant for the particular hormone or hormone derivative.

In another aspect administration of compositions of the present invention improves the uptake of the hormone and the hormone derivative component of the pharmaceutical composition in the blood of patients.

- 5 In another aspect the present invention provides pharmaceutical compositions which contain no solubilizers and which are low in or devoid of preservatives thereby avoiding irritation of the mucosa and minimizing damage to mucosal membranes caused by long-term use of said compositions.
- 10 In another aspect the present invention provides a method of prophylaxis or treatment of postmenopausal disorders or osteoporosis by using a transmucosal and in particular a nasal formulation of a drugs at a sufficient extent of adsorption.
- 15 It has, surprisingly, been found that alternative ways of administration of synthetic progestins, i.e. other ways than oral administration, although undergoing no first pass effect, also have advantages over the natural hormone.

The present invention provides a pharmaceutical composition for transmucosal
20 administration characterized in comprising an active ingredient being the natural sex hormone 17β -estradiol combined with a progestin which is selected from the group consisting of progesterone derivatives, $(9\beta,10\alpha)$ -6,7-didehydroprogesterone derivatives, 17α -hydroxy-progesterone and its derivatives, and 19-nortestosterone and its derivatives, dissolved in an oil constituting the incoherent
25 inner phase of an oil-water two-phase system, an emulsifying agent and, optionally, stabilizers. The progestins are 17α -hydroxyprogesterone, dydrogesterone, medroxy-progesterone and its acetate, medrogestone, chlormadinone and its acetate, norethindrone and its acetate, megestrol and its acetate, norgestrel, levonorgestrel, desogestrel, 3-keto-desogestrel, gestodene.

30 Preferred are dydrogesterone, medroxyprogesterone acetate norethindrone

acetate, desogestrel, 3-keto-desogestrel and gestodene. Most preferred is dydrogesterone.

In designing a drug for transmucosal drug administration and in particular
5 administration to the nasal mucosa special attention has to be paid to avoid irritation since such surfaces are very sensitive. Thus, surfactants and emulsifiers must be tolerated well and must show a very low rate of hemolysis. Other additives, which can include antioxidants, atonicity modifiers and preservatives should be such as are acceptable for parenteral application. Preservatives, in
10 particular, have a negative influence on the mucociliary clearance and on nasal tolerancy, and should therefore be avoided. A way of solving this problem is to construct emulsions which are autoclavable. The pharmaceutical compositions of the present invention are autoclavable and do not need preservatives if autoclaved.

15
Due to its ability to contain in a two-phase system, sufficient amounts although in very small volumes to be administered, strongly lipophilic derivatives of both 17 β -estradiol and derivatives of progesterone the pharmaceutical composition is particularly suitable for nasal administration, which is a convenient way of
20 administering drugs for therapy and treatment over extended periods of time.

The pharmaceutical compositions of the present invention solve the problem of avoiding degradation of 17 β -estrogen by first-pass mechanism by administering the hormone via mucous membrane. It solves, in the same way, the problem of
25 minimizing the dose of sex hormone derivative.

Effective doses of the emulsion of the present invention will result in serum levels of 17 β -estradiol of 20-200 pg/ml.

30 Depending on the kind of derivative the ratio progestin or progestin hormone/estrogen will generally be between 0.1/1 and 100/1 by weight.

The data below are examples of the proportions of hormones and hormone derivatives in pharmaceutical compositions of the present invention. Percentage figures are, all, by weight of the total emulsion.

5

| | Range | Preferred range |
|-----------------------------|------------|-----------------|
| Medroxyprogesterone | 0.01-0.25% | 0.02-0.1% |
| Medroxyprogesterone acetate | 0.01-0.35% | 0.02-0.1% |
| 10 Dydrogesterone | 0.05-1.4% | 0.1-0.8% |

As single doses of the active ingredients can be stated:

| | Range | Preferred range |
|-----------------------------|-----------------|------------------|
| 15 17 β -Estradiol | 5-200 μ g | 10-60 μ g |
| Medroxyprogesterone | 10-1000 μ g | 20-600 μ g |
| Medroxyprogesterone acetate | 10-1000 μ g | 20-600 μ g |
| Dydrogesterone | 50-5000 μ g | 100-3000 μ g |

20

Pharmaceutical compositions of the present invention should contain 5-50%, preferably 10-30% of the oleaginous vehicle constituting the oil phase and 0.7-6%, preferably 1-3% of the emulsifying agents. Antioxidants such as tocopherol can be added to 0.01-0.2%, preferably 0.02-0.1%. Tonicity modifiers such as sorbitol can be added to 270-320 mOsmol/kg, preferably 280-300 mOsmol/kg. A pH regulator such as NaOH can be added to pH 6-8, preferably to about 7.4 depending on the emulsifying agent and oil. Preservatives can be added if necessary. As one embodiment of the present invention can be mentioned:

25

1. The active ingredient, which is a combination of estradiol and progestins as described above, namely dydrogesterone, medroxyprogesterone, medroxyprogesterone acetate, chlormadinone acetate, norethindrone acetate, levonogestrel and desogestrel. Most preferred is dydrogesterone.

5

2. An oleaginous vehicle or oil phase containing 5 to 50% by weight of the composition of an artificial, semisynthetic or natural oil or, preferably, a mixture thereof. As examples of natural oils can be mentioned vegetable oils such as cottonseed oil, soy bean oil, castor oil, olive oil, almond oil or safflower oil. A semisynthetic oil component can be selected from the group consisting of middle chain triglycerides and mono acid triglycerides. Artificial oils can be polyoxyethylene ester of caprylic and capric acid and polyoxyethylated triglycerides.

15 3. Water.

4. A natural surfactant being a phospholipid such as egg lecithin or soy lecithin.

Optionally, stabilizers can be added such as:

20

5. An atonicity modifier such as glycerol, mannitol, xylitol, sorbitol, lactose or glucose.

6. A pH regulative agent such as sodium hydroxide or a salt of a long chain fatty acid such as sodium oleate.

25

7. An antioxidant such as DL- α tocopherol,

The pharmaceutical compositions of the present invention can be manufactured by dissolving the active ingredients in an oil phase, adding the emulsifier, optionally with the addition of a stabilizer (i.e. antioxidant), adding the water,

30

optionally with the addition of a stabilizer (osmolarity regulator) and, thereafter, homogenizing the two solutions to an emulsion.

The following are examples of pharmaceutical compositions for transmucosal
5 administration.

Example 1

| | | |
|----|-----------------------|------------|
| | 17 β -Estradiol | 0.050 g |
| 10 | Medoxyprogesterone | 0.055 g |
| | Triglyceride | 20.0 g |
| | Lecithin (soy bean) | 1.8 g |
| | NaOH (0.1 M) | 3.5 g |
| | Sorbitol | 3.3 g |
| 15 | Aqua ad inj. | ad 100.0 g |

Example 2

| | | |
|----|----------------------------|------------|
| | 17 β -Estradiol | 0.050 g |
| 20 | Medoxyprogesterone acetate | 0.075 g |
| | Triglyceride | 20.0 g |
| | Lecithin (soy bean) | 1.8 g |
| | NaOH (0.1 M) | 3.5 g |
| | Benzalkoniumchloride | 0.1 g |
| 25 | Sorbitol | 3.3 g |
| | Aqua ad inj. | ad 100.0 g |

Example 3

| | | |
|---|-----------------------|------------|
| | 17 β -Estradiol | 0.050 g |
| | Dydrogesterone | 0.28 g |
| 5 | Triglyceride | 20.0 g |
| | Lecithin (soy bean) | 1.5 g |
| | NaOH (0.1 M) | 3.5 g |
| | Sorbitol | 3.3 g |
| | Aqua ad inj. | ad 100.0 g |

10

Example 4

| | | |
|----|-----------------------------|------------|
| | 17 β -Estradiol | 0.050 g |
| | Medroxyprogesterone acetate | 0.070 g |
| 15 | Triglyceride | 18.0 g |
| | Soy bean oil | 2.0 g |
| | Lecithin (soy bean) | 1.5 g |
| | NaOH (0.1 M) | 3.5 g |
| | Benzalkoniumchloride | 0.1 g |
| 20 | Sorbitol | 3.3 g |
| | Aqua ad inj. | ad 100.0 g |

25

30

Example 5

| | | | |
|----|-----------------------|---------|------------|
| | 17 β -Estradiol | 0.04 g | |
| | Dydrogesterone | 0.325 g | |
| 5 | Triglyceride | | 20.0 g |
| | Tocopherol | 0.06 g | |
| | Soy bean lecithin | 1.9 g | |
| | Sorbitol | 3.3 g | |
| | NaOH (0.1 N) | 0.86 g | |
| 10 | Aqua ad. inj | | ad 100.0 g |

The pharmaceutical compositions as described above can be administered by nasal application. The amount of the liquid administered per unit dose and per nostril should be less than 0.2 ml.

15

The emulsion system according to Example 1 was prepared in the following way:

The active ingredients were dissolved in the oil phase. Tonicity modifier and cosurfactant were dissolved in the water phase. The phospholipid (for example
20 lecithin) was dissolved in the oil phase. The two phases were mixed and emulsified by a high speed shear mixer. The resulting, coarse, emulsion was then homogenized using a high pressure homogenizer until a fine monodispersed emulsion with a small range of droplet size was formed.

25

Biological Experiments

The experiment described below serves to illustrate the uptake of active ingredients in vivo upon nasal administration of a pharmaceutical composition
30 according to the present invention in sheep.

Mixed breed adult sheep were used for the animal experiments. The emulsion formulation of Example 5 containing 17β -estradiol and dydrogesterone was administered to six sheep by application of 0.14 ml of a nasal spray into each nostril. The given dose was 108 μ g of 17β -estradiol and 910 μ g of dydrogesterone.

- 5 Prior to administration blood samples were taken from all animals. After application blood samples were taken from the cannulated external jugular vein at 0, 5, 10, 20, 30, 45, 60, and 120 minutes.

- 10 Samples were kept at room temperature for approximately 30 minutes to initiate clotting before centrifugation for 5 minutes at 1800 rpm and stored in the refrigerator prior to collection of serum. Serum was pipetted into cryo-tubes and stored at -70°C . Estradiol serum levels were determined by enzyme immunoassay using an Amerlite Estradiol-60 Assay® with a measurement range of 0 - 4086 pg estradiol/ml. Dydrogesterone was determined by gas chromatography-mass
- 15 spectrometry (GC-MS).

- Mean values of the maximum plasma concentration and the time after which the maximum plasma concentration was reached and the standard errors of mean after nasal administration of estradiol and dydrogesterone are given in Table 2a
- 20 and 2b below. The areas under the absorption curves (AUC) were calculated from 0 minutes to 120 minutes using the trapezoidal rule. The results show that a remarkable plasma level could be reached by nasal application of about 108 μ g 17β -estradiol and 910 μ g dydrogesterone dissolved in the emulsion formulation. The maximum plasma level of 375 pg estradiol/ml 10 minutes after application
- 25 decreases to 70pg/ml after 120 minutes. The nasal dose of about 100 μ g 17β -estradiol results in an estradiol plasma level equivalent to the luteal phase of the female menstrual cycle which is desired for the treatment of osteoporosis and postmenopausal disorders. A pronounced absorption after nasal application can also be observed for dydrogesterone. The plasma concentration of dydrogesterone
- 30 decreases from 1011pg/ml to about 56 pg/ml after 120 minutes.

**Table 2a: Plasma concentration of estradiol after nasal application of 108mg
17 β -estradiol to 6 sheep**

| | Mean value | Standard deviation |
|----------------------|------------|--------------------|
| 5 AUC (pg min/ml) | 13965.0 | 5438.2 |
| Maximal conc.(pg/ml) | 374.8 | 263.1 |
| t max (min)10.0 | 5.5 | |

Table 2b: Plasma concentration of dydrogesterone after nasal application of 910

10 μ g to 6 sheep

| | Mean value | Standard deviation |
|-----------------------|------------|--------------------|
| AUC (pg min/ml) | 34968.5 | 17216.3 |
| Maximal conc. (pg/ml) | 1011.2 | 561.9 |
| t max (min) | 16.0 | 5.5 |

Claims

1. A pharmaceutical composition for transmucosal administration, which composition is an oil-in-water emulsion, containing, dissolved in the dispersed oil
5 phase, the natural sex hormone 17β -estradiol together with a progestin, which is selected from the group consisting of progesterone derivatives, 17α -hydroxyprogesterone and its derivatives, $(9\beta, 10\alpha)$ -6,7-didehydroprogesterone and its derivatives, and 19-nortestosterone and its derivatives.
- 10 2. A pharmaceutical composition according to claim 1 for nasal administration.
3. A pharmaceutical composition according to claim 1 for buccal administration.
4. A pharmaceutical composition according to any of claims 1 to 3 characterized
15 in that the progestin is a derivative of $(9\beta, 10\alpha)$ -6,7-didehydroprogesterone.
5. A pharmaceutical composition according to any of claims 1 to 4 characterized in that the progestin derivative is dydrogesterone.
- 20 6. A pharmaceutical composition according to any of claims 1 to 5 characterized in being sterilizable by autoclaving.
7. A pharmaceutical composition according to any of claims 1 to 6 characterized in being in the form of sterile unit dose or multidose packings.
25
8. A pharmaceutical composition according to any of claims 1 to 7 for use in therapy.

9. A process for the manufacture of a pharmaceutical composition according to any of claims 1 to 8 characterized in dissolving the active ingredients, an emulsifier and, optionally, an antioxidant in an oil phase, adding the water phase optionally containing dissolved atonicity modifier an/or pH-regulator and,
5 thereafter homogenizing the two phases to prepare an emulsion.
10. The use of a pharmaceutical composition according to any of claims 1 to 7 in the manufacture of a medicament for providing a measurable serum level of the active ingredients.
- 10 11. The use of a pharmaceutical composition according to claim 10 wherein the serum level of 17β -estradiol is 20-200 pg/ml.
12. The use of a pharmaceutical composition according to any of claims 1 to 7 in
15 the manufacture of a medicament for the treatment of postmenopausal disorders.
13. The use of a pharmaceutical composition according to any of claims 1 to 7 in the manufacture of a medicament for the treatment of osteoporosis.
- 20 14. The use of a pharmaceutical composition according to any of claims 1 to 7 for providing a measurable serum level of 17β -estradiol.
15. The use of a pharmaceutical composition according to claim 14 wherein the serum level of 17β -estradiol is 20-200 pg/ml.
- 25 16. The use of a pharmaceutical composition according to any of claims 1 to 7 in the treatment of postmenopausal disorders.
17. The use of a pharmaceutical composition according to any of claims 1 to 7 in
30 the treatment of osteoporosis.

18. A method for the treatment of postmenopausal disorders comprising the administration of an effective amount of a pharmaceutical composition according to any of claims 1 to 7 to a patient in need of such treatment.
- 5 19. A method for the treatment of osteoporosis comprising the administration of an effective amount of a pharmaceutical composition according to any of claims 1 to 7 to a patient in need of such treatment.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/01102

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/107, A61K 31/565, A61K 31/57
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, WPI, MEDLINE, JAPIO

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| P,X | WO 9422426 A1 (AKTIEBOLAGET ASTRA), 13 October 1994 (13.10.94) -- | 1-17 |
| X | EP 0391369 A2 (YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM), 10 October 1990 (10.10.90), page 3, line 45 - page 5, line 33 -- | 1-17 |
| X | STN International, Derwent Information Ltd, WPIDS accession no. 89-064960, Asahi Chem Ind Co Ltd: "Prepn. of emulsion formulations enclosing drugs - which are slightly soluble in water and oil, by kneading drug with an oil in presence of phospholipid before emulsifying", & JP, A, 01016716, 890120 (8909) -- | 1-17 |

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

- * Special categories of cited documents:
- * "A" document defining the general state of the art which is not considered to be of particular relevance
- * "B" earlier document but published on or after the international filing date
- * "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- * "O" document referring to an oral disclosure, use, exhibition or other means
- * "P" document published prior to the international filing date but later than the priority date claimed

- * "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- * "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- * "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- * "&" document member of the same patent family

Date of the actual completion of the international search

6 February 1996

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. +46 8 666 02 86

Date of mailing of the international search report

07 -02- 1996

Authorized officer

Anna Sjölund
Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 95/01102

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| A | EP 0461290 A1 (HENNING BERLIN GMBH CHEMIE- UND PHARMAWERK), 18 December 1991 (18.12.91) -- ----- | 1-17 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 95/01102

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18-19
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

05/01/96

International application No.
PCT/SE 95/01102

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|--|--|
| WO-A1- 9422426 | 13/10/94 | NONE | |
| EP-A2- 0391369 | 10/10/90 | AT-T- 110563 AU-B,B- 614465 AU-A- 5292790 CA-A,C- 2013755 DE-D,T- 69011922 JP-A- 2290809 US-A- 5364632 | 15/09/94 29/08/91 11/10/90 05/10/90 12/01/95 30/11/90 15/11/94 |
| EP-A1- 0461290 | 18/12/91 | SE-T3- 0461290 DE-D- 59004243 | 00/00/00 |